APPLIED ORGANOMETALLIC CHEMISTRY, VOL. 6, 3–18 (1992)

REVIEW

Tin in pharmacy and nutrition

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The occurrence of tin in plants, animals and humans is discussed in relation to its abundance in the lithosphere and hydrosphere and the range of different tin(II) and tin(IV) complexes formed. A reasoned consideration of the essentiality or otherwise of tin for living species is given and it is concluded that tin is beneficial even if not yet proved to be an essential element.

After reference to the chemistry of tin compounds, there is a detailed discussion of their toxicity in animals and humans. Feasible routes for tin intake and uptake into humans are described.

The use of tin pharmaceuticals in previous and current times is reviewed and areas for which they are currently permitted for use in man as dentifrices and mouth washes, as radiopharmaceuticals and for the treatment of jaundiced newborns are described. A detailed review of tin-coating antitumour agents as representative tin pharmaceuticals is given.

Finally, a range of tin compounds having other specific pharmaceutical applications and which are currently being investigated are listed.

Keywords: organotin, tin, toxicity, essential elements, radiopharmaceuticals, dentifrices, tinhaem, antitumours, antimalarials, bactericidals, antihelminthes

1 INTRODUCTION

The abundance of tin in the Earth's crust is estimated to be 40 ppm and is higher than cobalt (23 ppm) and molybdenum (15 ppm) but lower than copper (70 ppm) and zinc (132 ppm), all these four metals being essential trace elements to humans. Tin is actually the 29th element in abundance for the elements in the Earth's crust, lithosphere and hydrosphere.

Tin is ubiquitous in nature, being found throughout the Earth's surface at a few parts per million. This assumes that extremely precise and advanced analytical methods are available for its detection.[1] In the soil, tin is usually found present at 3–6 ppm,[2] and at slightly higher values in rocks.[3] The concentration of tin in soil is invariably greater than that of cobalt and molybdenum.[4] In the hydrosphere, however, tin concentrations are far lower. Tin in ocean waters varies around an average 0.01 ppb.[5] Values higher than 5 ppm are indicative of pollution having occurred. In rivers, the dissolved tin content ranges from 0.3 to 17 ppb.[6] Tin in water supply reservoirs of most European and American cities is similarly low, ranging from 0 to 0.1 ppm.[7,8]

Thus it may be concluded that tin concentrations in the geosphere (with the exception of ore deposits and anthropogenically polluted areas) are uniform and low. Nevertheless, these are the main sources for intake into humans. It is noteworthy that air contains $(12–800) \times 10^{-9}$ g m^{-3} of tin, which arises from volcanic emissions, from industrial activities, from combustion of fuels, from continental dust-storms and from forest fires.[9] This is an alternative route of intake for living organisms and especially for rodents.[10]

Tin occurs in the tissues of a range of plants. Average values for the percentage of tin in plants are elusive since the concentration is both species- and organ-dependent. Vegetables are found to have 0.2–9.92 ppm,[11] but 1.5–32 ppm may be analysed from some other species.[12] Generally, tin concentrates predominantly in plant roots.[2] Millman found no simple correlation between the concentration of tin in soil and in the plants of the same area.[13] Environmental contamination arising from tin-canning or from organotin agrochemicals does not have an apparent effect upon the occurrence of tin in plants.[2,12] Thus, plant tin levels can be assumed largely to be a natural phenomenon rather than an anthropogenic occurrence.

Though the presence of tin in plants is considered to be ubiquitous, the biological requirement for tin as an essential nutrient for plants has

0268–2605/92/010003–16 $08.00

Received 20 June 1991
Accepted 24 September 1991

not yet been unequivocally established. There is only one indication of the involvement of tin in plant physiology.[14] In some trees, tin is accumulated in the leaves, which indicates a distant and reasonably rapid transport from the soil upwards. This kind of movement necessitates the presence of a soluble form of tin. Soluble inorganic tin compounds are generally toxic, and thus not beneficial for plants. It may therefore be expected that an organic soluble tin complex compound is responsible for the transporation observed. To date, no tin organic compound has been identified from plants. Curtin *et al.*[14] have reported important indirect evidence that a soluble volatile organic-tin compound participates in the biochemistry of coniferous trees, through findings of 23–80 ppm tin in the ashed residues of the vapours transpired from the leaves of this type of plant.

Tin has been found to be quite widespread in the tissues of animals. Marine animals show a strong accumulation of tin. Powerful accumulators are echimodermata (800 ppm) and Gastropoda (250–150 ppm).[15] The function of tin in these beings is unknown. However, they clearly concentrate tin from that naturally occurring in the oceans. For the terrestrial animals, very little analytical work has been reported for the tin content in different organs. The most precise analytical work for tissue tin contents has been performed using laboratory rats and mice.[16,17]

Tin spectrographic emission analysis of human tissues carried out by Teraoka[18] revealed high tin concentration in the hilar lymph mode (9.9 ppm), whilst Cardarelli found that the highest level of tin in humans is in the thymus gland.[17] In humans, whole blood contains 14 μg tin per 100 g and is concentrated in the erythrocytes.[19]

The accumulation of tin in thymus and in the lymphatic system suggests an immune involvement of tin in animals.[20] It is useful to note that little or no detectable tin has been found in foetal or newborn tissues.[21] However, the amount of tin increases rapidly in the first year of life and afterwards remains almost constant; unlike many other metals, it does not accumulate with age. Even though tin is ubiquitous in animal tissues, its essentiality has not been definitively proven.[22–24] To date, no essential function has been shown to be tin-dependent. Similarly, biochemical pathways have not been reported. In 1970, Schwartz *et al.*[25] reported that various tin compounds stimulated growth in weanling rats fed with highly purified diets and protected from contamination with environmental trace elements. It was also suggested that this growth stimulation might apply to humans. However, there are no further reports of independent evidence to confirm Schwartz's suggestions.

The chemical forms in which tin participates in the biochemical processes in animals and plants are unknown. Despite the lack of direct evidence for the tin function in animal physiology, some tentative proposals should be given. Tin, in either the +II or the +IV oxidation state, is able to form soluble complexes with biological molecules, for example with amino-acid anions,[26] proteins,[27] nucleosides,[28] carbohydrates[29] and steroids.[30]

In animals, there is rapid transport of tin intake to different organs and such movement ought to be facilitated by soluble complexes which are stable at physiological pH values.

The oxidation potential for $Sn^{2+} \rightarrow Sn^{4+}$ is -0.154 V (compared with the standard hydrogen electrode). This value lies within the physiological range and is close to the oxidation–reduction potential values of several flavin-enzymes. This may imply a possible involvement of tin in some enzymatic processes.[23] Cardarelli[31] explained his findings of high percentages of tin in the thymus glands of rats and humans by suggesting that it is this gland which produces one or more biochemical compounds of tin. Active tin compounds possibly include tin steroids or tin peptides, since steroids and peptides are active hormones participating in thymus immune function.[16,32] It has been proposed that these tin complexes function as hormones suppressing carcinogenesis.[33,34] This hint of a specific biochemical function for tin *in vivo* has not been extensively verified by experimental data. Thus, for judging whether tin is essential for humans in relation to cancer prophylaxis, the evidence is still incomplete.

2 AN OUTLINE OF THE CHEMISTRY AND TOXICITY OF TIN

Tin compounds occur in oxidation states II and IV. The most important oxidation state is IV. The outstanding feature of the chemistry of tin(II) compounds is the ease of their oxidation up to tin(IV). In particular, solutions of tin(II) which do not contain sufficiently strong electron donor species equivalent to fluorides, for example, are

rapidly oxidized by relatively mild conditions such as atmospheric oxygen. Thus, the most stable tin compounds belong to the IV oxidation state. Very few organotin(II) compounds bearing carbon–tin σ-bonds, for example $(R_2Sn)_n$, are known, as they are substantially less stable than the plethora of known organotin(IV) compounds.

Both tin(II) and tin(IV) form simple compounds which include oxides, halides, sulphates, phosphates, carboxylates and alkoxides. The structures of tin(II) compounds vary between angular, square pyramidal, trigonal pyramidal and octahedral. Tin(IV) structures are tetrahedral, trigonal pyramidal or octahedral. In addition to the simple tin(II) and tin(IV) compounds listed above, many coordination and chelate compounds are known. These can be quite stable in both oxidation states. Tin, in both oxidation states, forms coordination complexes with donor atoms such as halogens, oxygen, nitrogen and sulphur. The best known organotin compounds which are of relevance to the present paper are the dialkyl- and trialkyl-tin(IV) compounds having the general formulae R_2SnX_2 and R_3SnX, respectively, where R = alkyl or aryl radicals, and X = halogen or other electron donor species. In the R_3SnX species, trigonal bipyramidal (five-coordinated) structures prevail, whilst in the R_2SnX_2 complexes octahedral structures occur. Useful reviews on the chemistry of bivalent[35] and tetravalent[36, 36a] tin have been published and there is also a valuable recent monograph on tin chemistry.[37]

In the rest of the present paper, we refer to (i) simple tin compounds, (ii) coordination tin compounds, and (iii) organotin compounds.

The toxicities of different tin compounds differ markedly. Simple tin compounds, including tin metal, have low oral toxicity.[38, 39] LD_{50} values for tin(II) chloride ($SnCl_2$) in rats and mice are 700 to 1200 mg kg^{-1}, respectively.[40] The underlying reason for the low toxicity of tin salts and especially of the oxides and sulphates is their poor absorption from the alimentary tract.[21, 41, 42] The rate of absorption of tin(II) in ionic form (from salts) from the gastrointestinal tract is reported to be 2.85 % of the dose;[43] even less (0.64 %) is absorbed when tin is administered as tin(IV) salts. The difference in the uptake between tin(II) and tin(IV) is presumably due to the greater insolubility of tin(IV) species.[44]

No change in oxidation state occurs during absorption by organisms, i.e. tin is largely absorbed and transported in the oxidation state in which it was ingested.[43] It is a generally accepted principle of chelation therapy and of metallo-drug administration that only neutral complexes traverse the hydrophilic phospholipid membrane of the intestine.[45] This explains the low oral toxicity of the simple tin compounds.

Tin is classified as a Type III element in Bowen's classification of toxicity,[44] being absorbed less than 5 % across the gut wall.[46] Contrary to the hypothesis that only net-neutral tin species are bioavailable, De Groot[39] suggests that toxic effects in animals may be induced by the intake of simple tin compounds bearing positive charge. The transport of these cationic forms may possibly be due to the ability of living cytoplasm to function as a cation exchanger and to retain the cationic tin.

Animal data have shown that soluble salts of tin are gastric irritants. Rats fed with 0.3 % or more concentrated solutions of tin salts suffered growth retardation, reduced haematocrit values, and haemoglobin levels.[39] Generally, tin is believed to have a destructive action upon blood corpuscles and may cause degradation of haem.[47] In practice, tin injected into rabbits increases the concentration of coproporphyrin in blood and urine.[48] This suggests that tin interferes in the biosynthesis of porphyrin and its involvement in enhancement of haem breakdown. Kappas and Main[49] reported that injection of stannous chloride into animals induce haem oxygenase activity in both liver and kidney and that an acceleration of haem breakdown occurs. These data explain the anaemias reported.[39] Tin also inhibits the activity of 5-aminoevulinate dehydrase in blood.[39]

Tin antagonizes the absorption and metabolism of several essential metals such as calcium,[50] zinc, copper and iron[51] in rats. Effects upon calcium biochemistry are also observed in humans.[52] Tin depresses the absorption of selenium in man, an observation which may be related to selenium deficiencies.[53] Dialysed uraemic patients showed abnormally high concentrations of tin in tissues; however, even this tin may not be definitively xenobiotic since there is a powerful inducement of haemoxygenase activity in the kidneys.[54]

It is noteworthy that diets containing high levels of tin produce anaemia in rats unless high levels of iron and copper are co-administered. This supplement does not arrest growth depression. Therefore, two mechanisms are apparently associated with the action of the subacute toxicity of tin in animals, one affecting the growth and the other haemoglobin synthesis.[55]

Reports of poisoning in man arising from simple tin compounds are relatively rare. Except from their natural tin content, foods from plants and animals possibly accumulate extra tin from the canning process. It was reported that certain canned foods and drinks in several countries contain from 250 to 700 ppm of tin and have caused nausea, vomiting and diarrhoea in a large number of individuals.[56–61] Concentrations higher than 1000 ppm are definitely considered dangerous to humans.[56] It was also observed that a prolonged exposure to tin overdose decreases efficiency of absorption from the intestine.[43] For food poisoning from cans, tin citrates[62] and tin malates[63] are usually blamed for the symptoms. However, symptoms arising from staphylococcal toxins are similar to those of tin poisoning and so diagnostic confusion can occur.[64]

Tin in the lungs is accumulated by inhalation rather than ingestion.[43] Long-term inhalation of tin oxide, in rare instances, causes symptomless benign pneumoconiosis, known as stannosis.[65–67] Inorganic tin is poorly absorbed by the human body; 1–3 % of the ingested tin remains in the human body whilst the remainder is rapidly excreted in the faeces and through the urinary tract.[52,68] Urinary excretion of tin is rather low, amounting to just 4–246 $\mu g\,day^{-1}$, regardless of the dietary intake.[69] This is probably due to the fact that the preferred route for tin extraction is through the bile and pancreatic juices or, alternatively, through perspiration. Sites of xenobiotic tin in the human body are bones, lymphatic nodes, lungs and, to a lesser extent, liver, kidneys and the cells of the small intestine.[21,43,61,70] Xenobiotic tin is not found in the brain since it is excluded by the blood–brain barrier (unless present as organotins) and is also not foetotoxic owing to low transplacental transfer.[21]

In contrast, organotin compounds are extremely toxic (particularly the trialkyl derivatives) to all animals and humans. For example the LD_{50} value for $(Et_3Sn)_2SO_4$ is about $6\,mg\,kg^{-1}$.[71] The lower trialkyls show the highest toxicity.[72–76] As the alkyl radical has an increasing carbon content, the toxicity decreases markedly so that the n-octyl analogues are essentially non-toxic.

The lower trialkyltins are powerful neurotoxic agents and may cause paralysis and death. The mono- and di-alkyl derivatives are of very low toxicity. Tetra-alkyltins are also toxic because they are converted enzymatically *in vivo* to trialkyltins and so their toxicity is slow-acting.

Most dialkyl tin chlorides are relatively toxic to rats, depending on the route of administration. For example, $n\text{-}Bu_2SnCl_2$ and $n\text{-}Oct_2SnCl_2$ and, to a lesser extent, Et_2SnCl_2 and $n\text{-}Pr_2SnCl_2$ induce reduction of the thymus weight of rats at dietary levels of 10 and 150 ppm.[77,78] Orally, the acute toxicity of dioctyltin compounds is rather low as Oct_2SnCl_2 has an LD_{50} value of $8500\,mg\,kg^{-1}$;[79] this suggests that dioctyltin compounds given orally are biologically unreactive to animals and humans.[80] In contrast, dioctyltin compounds when administered to rats by the intravenous route have LD_{50} values below $10\,mg\,kg^{-1}$.[71]

All organotins are capable of disturbing the gastrointestinal tract, depending upon concentration and speciation.[81] Acute effects of organotin poisoning have been observed in the brain, liver and kidneys of rats.[82] Irritant dermatitis has been observed by human contact with $(Bu_3Sn)_2O$ (TBTO).[83] The toxicity of organotin compounds much depends upon the nature of the chemical moieties and groups contained in the alkyl or phenyl groups of the organotins.[84,85] The biochemistry of action of organotins and their physiological functions in the animals is complex.[86–88] Triethyltin is a powerful inhibitor of mitochondrial oxidative phosphorylation.[89] Further details of toxicities are given in Ref. 37.

3 ROUTES FOR TIN INTAKE INTO HUMANS: THE TIN CYCLE IN THE BIOSPHERE AND GEOSPHERE

Given that the legal permissible level of tin in canned foods in the UK is 250 ppm,[90] the operational limit is set at 200 ppm in canned foods and drinks.[91] Undoubtedly, canned foods are the main source of tin in human diets, but there are also other routes of intake of secondary importance.

Tin compounds have long been used as stabilizers in the manufacture of plastic bottles and films.[92] Acid juices or vinegar may leach such tin to a significant level from these containers.[93]

Tin may migrate from tinfoil used for food wrapping; this is particularly so with cheeses, which possibly accumulate up to 2000 ppm tin.[94] Ishiwata[95] reported an unusual route to explain the presence of tin in several foods which involved migration from tableware. The experiments were carried out in 4 % acetic acid in the temperature range 60–100 °C and 3–9.9 ppm migration levels were detected.

Tin is also contained in bottle caps from the

stabilizers and plasticizers.[96] Food contamination from such sources is minute but this contamination is potentially dangerous because it involves organotins.

Tin is a constituent of phosphate fertilizers,[21] of different agrochemicals and of biocides.[97–100] It is important to note that organotins used as biocides in agriculture will not be absorbed in considerable amounts into plants because of the low bioavailability of tin. Such tin compounds already present at extremely low concentrations then enter by the food cycle into animals and humans in minute amounts. Analysis of plant tissues has not shown any sizeable accumulation of tin over the last few years.[101]

One possible way that organotins enter into food cycles, particularly in recent years, is via urban water supplies, owing to the draining of agrochemicals and from plastic water pipes. The river fluxes of tin to the oceans is 0.76×10^6 mol yr^{-1} for the dissolved fraction and $(300–600) \times 10^6$ mol yr^{-1} for the particulate fraction.[102] Regretably, recent analyses are generally absent for the tin and organotin contents of water reservoirs of urban areas.[103] It has been shown that organotin compounds may be degraded in sediment.[104] Trialkyltins, in particular, degrade slowly to virtually non-toxic monoalkyltin derivatives in the presence of sunlight or of marine micro-organisms.[105–108] With the exception of agrochemicals, another anthropogenic source of tin in water is urban sewage. Fortunately, this immobilizes a large amount of tin in the sediment column.[109] These reports lead us to suggest that tin does actually enter the food cycle in humans but only in minute amounts. Thus, in general, dangerous forms are not present from canning, or from potable water and foods.

Over the last 25 years, organotins have been added to ships' paints to prevent the attachment of ocean plants and animals (barnacles, seaweeds, worms, blue and green algae, etc.). The usual antifouling agents are tributyltin oxide (TBTO) and tributyltin fluoride (TBTF). TBTO is extremely toxic to marine biota such as molluscs, scallops, oysters[110–114] and perhaps fish.[115, 116] Most commonly, experiments were carried out using mussels (*Mytilus edulis*). Mortality was evident in these species whereby half of the larval population of mussels was dead by 15 days, when subjected to contact with 0.1 μg dm^{-3} TBTO. Therefore, the 15-day LD_{50} value appears to be 0.1 μg dm^{-3} for TBTO for these particular species gathered in the UK.[111] A value of 0.97 μg dm^{-3} was also reported as the LD_{50} value for mussel specimens from the USA,[117] i.e. adverse biological effects occur at low concentrations.

Considerable differences in LD_{50} for TBTO appear to exist between various marine genera and species.[118]

The larval stage of the common mussel appears to be the most sensitive stage for TBTO. TBTO and TBTF, although their physiological mechanism in marine animals is not fully elucidated, affect oxidative phosphorylation by the inhibition of energy metabolism in the mitochondria of such marine animals as barnacles (*Balanusam phitrite amphitrite*).[119] Even sub-lethal doses for sea animals have had great commercial consequences upon the shellfish and fishing industries.[120]

Antifouling agents slowly dissolve from paints on boats and pollute the seawater in the vicinity of harbours, estuaries and beaches, etc.[121] The use of TBTO is banned for small boats in the UK, USA, Republic of Ireland and France. TBTO is permitted only for ocean-going vessels.[5] Nevertheless, there is a persistent intake into fish and other sea creatures with the result that seafoods are an important route for tin to enter the food chain in humans. The GESAMP (Group of Experts on the Scientific Aspects of Marine Pollution, a UN organization) evaluation showed that seafood contribution to the daily intake of tin for man is low and not a public health problem, even in moderately polluted areas.[122]

Finally, there is a minor intake of tin from cosmetics (dentifrices and mouth washes) and possibly from pharmaceuticals for external use such as germicides. These topics will be discussed later.

It is clear that the most important source of tin for human intake is canning,[123] wherein the tin possibly arises from any of the previously reviewed cases, each of which has the potential to become important. This may be summarized in a schematic diagram of the tin cycle in the geosphere and biosphere (Fig. 1). No quantitative details for the tin fluxes in the tin biogeochemical cycles are known.

4 TIN PHARMACEUTICALS

In the past, there has been only limited use of tin compounds as pharmaceuticals. Frouin and Gregoire[124, 125] first suggested in 1917 that tin, tin oxide, tin(II) chloride and sodium stannate had

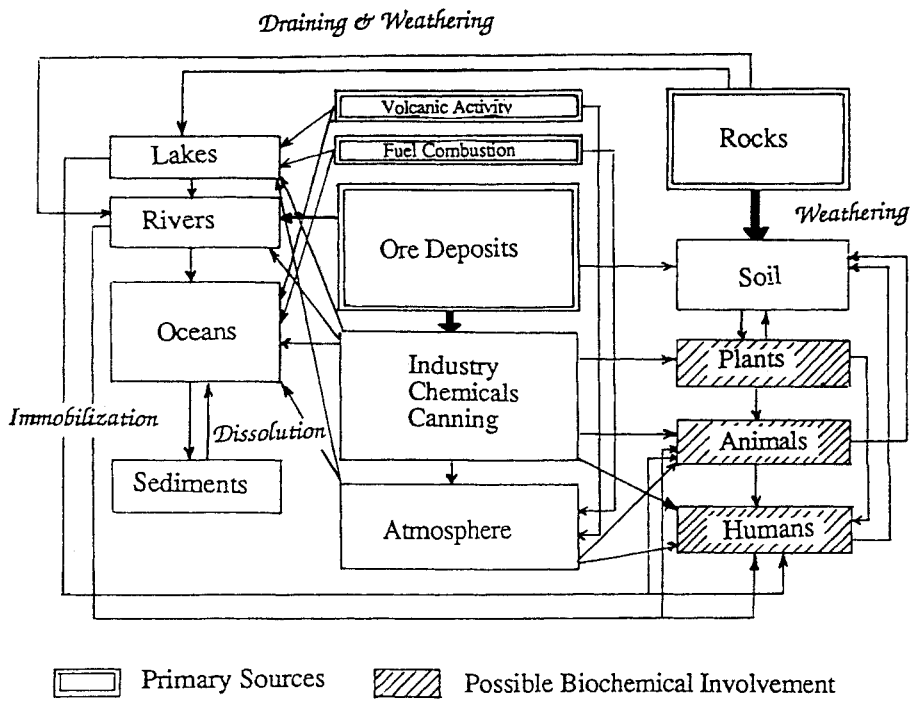


Figure 1 The tin cycle in the geosphere and biosphere.

positive activity against staphylococcal virulence. However, subsequent work[126,127] indicated that neither soluble nor insoluble tin compounds had any appreciable effect either *in vitro* or *in vivo* on staphylococcal activity in rabbits or humans.

Nevertheless, the concept that normal stannous salts have some value in the control of cutaneous sepsis persisted, possibly because simple tin compounds have definite germicidal and bacteriostatic activities.

In 1954, a serious condition afflicted users of a French pharmaceutical preparation trade-named 'Stalinon' containing diethyltin di-iodide. The drug had, in fact, been accidentally contaminated with toxic triethyltin iodide, causing celebral oedema to animals and humans; 217 individuals were poisoned, of whom 110 died.[71,92,128,129] Since then, confidence in tin drugs has been seriously depressed. In the UK over the last 50 years, only two tin-containing drugs were marketed. One, 'Staniform', was a preparation containing methyl stannic iodide as an external treatment drug for staphylococcal infection.[130] This preparation was in use until 1958. The second drug was 'Stannoxyl' and contains tin powder and tin(II) oxide in the form of tablets for oral treatment against various skin disorders and other abnormalities such as acne, boils, carbuncles and styes.[131] The preparation was used until the early 1980s.

In the remainder of this review, tin drugs and cosmetics in use today will be discussed, and then reference will be given to potential new drugs under investigation.

4.1 Tin pharmaceuticals licensed for use

4.1.1 Dentifrices and mouthwashes

Tin(II) fluoride (SnF_2) has been used since 1947 in dental healthcare as a protective agent against dental enamel dissolving in lactic acid,[132] and tin is more effective than sodium fluoride.[133] It was later shown that SnF_2 was superior to all other fluorides for the inhibition of dental plaque formation.[134–136] For almost the last 50 years, SnF_2 has been incorporated into dentifrices, mouthwashes, topical solutions and, occasionally, into dental cements.[137] SnF_2 appears to have both prophylactic and therapeutic effects on plaque formation. In combination with acidified phosphatofluoride (APF), it controls dental caries

formation, inhibits dental plaque growth, moderates root hypersensitivity and reduces root surface solubility. There are several reviews describing the beneficial action of SnF_2 on dental caries.[138–143]

Only the tin(II) ion has an antibacterial effect and it is the main agent for plaque prevention and suppression, whereas the fluoride ion does not contribute to this activity.[141,144] It has been reported[145] that a differentiation exists between the antimicrobial and anticaries action of $SnCl_2$ and SnF_2 *in vivo* and *in vitro*. *In vivo*, such activity is only slight for $SnCl_2$, but both SnF_2 and $SnCl_2$ have considerable activity against oral micro-organisms *in vitro*.[146] It is possible that such differences can be attributed to the difficulty in keeping stannous ions, i.e. $SnCl_2$, in solution in the mouth. A general potential difficulty arises in the use of tin(II) in oral hygiene; the tin(II) ion is very easily hydrolysed and usually precipitates in the course of its action in the mouth membranes. The tin(II) ion is also easily oxidized to the tin(IV) ion, which is inactive as a bacteriostatic agent hence the use of the less soluble SnF_2 rather than $SnCl_2$.

To overcome these difficulties, the older method was to add to the oral preparation glycerol, sugars and gums.[147,148] The more modern method of avoiding technical difficulties in the action of the SnF_2 on plaque is to add a complexing agent to the dentifrice or mouthwash preparation. A stannic coordination complex is obtained which is stable to hydrolysis and oxidation and slowly releases tin(II) into the mouth membranes. It is also advantageous if the complexing agent has mild bacteriostatic properties.[149]

Tin(II) pyrophosphate ($Sn_2P_2O_7$) has also found wide application in topical dental therapy for more than 15 years.[150]

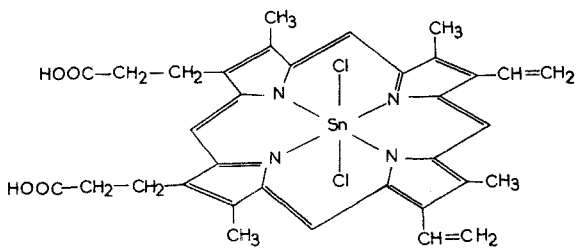
The mechanism of the reaction between SnF_2 or $SnCl_2$ with dental enamel has not yet been fully elucidated. Scanning electron microscopy (SEM) and electron microscopy have been applied to this problem.[151,152] It seems probable that a non-stoichiometic compound, approximating to Ca_2F_6, in the form of globules is formed in enamel and this is put forward as responsible for the caries treatment; this explanation is not without doubt since other workers[153] postulated a tin species of formula $Sn_{10}(PO_4)_6(OH)_{2-n}$, where $1 < n < 2$, for the SnF_2–enamel interaction. No structural evidence is known for the last compound. Another viewpoint, which holds mostly for tooth fillings, is that tin forms complexes with the major tooth protein collagen to form tin chains and/or lattices as found in the *in vitro* experiments.[154] Dibutyltin dilaurate and tin(II) acetate have been used as catalysts in vulcanizing silicon rubbers for prosthetic uses in dentistry. These compounds, if included after polymerization of the rubber, can act as inhibitors of the growth of *Candida albicans* germs usually present under such conditions.[155]

4.1.2 Use of tin in radiopharmaceuticals

Tin salts such as $SnCl_2.2H_2O$, SnF_2, $Sn_2P_2O_7$, $Sn(OH)_2.xH_2O$ have been used for the last 15 years as routine diagnostics in connection with metastable technetium-99 (^{99m}Tc) as a scanning agent in scintigraphy. Liver, pancreas, spleen, kidney, heart, gall bladder, lung and skeletal scintigraphy can easily be effected by ^{99m}Tc because of the optimum nuclear properties of this nuclide.[156] The tin(II) involvement in the procedure consists in the reduction of the pertechnetate(VII) anion $[^{99m}TcO_4]^-$ to $^{99m}Tc^{4+}$ or ^{99m}Tc (metal–colloid). In the process, a complexation ligand (L) should always be present to coordinate with both Sn^{4+} and $^{99m}Tc^{4+}$ with the production of a mixed $^{99m}Tc^{4+}$–Sn^{4+}–L complex which subsequently it is to be the carrier of the metastable technetiumn-99 to the specific organ under examination. $SnCl_2$ in hydrochloric acid is used for the reduction in most cases. For the complexing agent, the following compounds can be used: 2,6-diethylphenylcarbamoylmethyliminoacetic acid, diethylenetriaminepenta-acetic acid, dimercaptosuccinic acid, methylendiphosphonic acid, different amino acids, pyroxilideno-amino acids, blood serum albumin, fibrinogen, plasmin, heparin, salicylideno-amino acids and others, depending on the case under diagnosis.

A large number of literature citations exist describing the technique. Some representative papers are cited.[157–163] It is interesting to note that the technique can also be applied to labelling red blood cells using tin(II) pyrophosphate.[164]

A newly introduced radiochemical preparation containing tin is employed for the treatment of multiple metastatic loci in bones. Analogously to ^{99m}Tc–tin diphosphonate scanning, reduction from $[^{186}ReO_4]^-$ by Sn^{2+} in the presence of hydroxyethylidene diphosphonate occurs, and a rhenium-186(tin)hydroxyethylidenediphosphonate complex is prepared which localizes in the metastatic loci of bones and delivers the appropriate therapeutic radiation[165] to the malignant cells. The technique of metastable technetium-99 scintigraphy aided by suitable ligand complexation,



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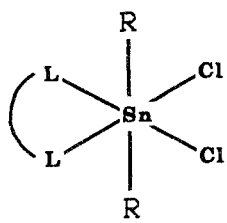
with the simultaneous action of Sn^{2+} as reducing agent, is under further investigation with a view to wider clinical use.

4.1.3 Tin-haem as a therapeutic agent for treating jaundice

Hyperbilirubinaemia is an abnormality observed mainly in the newborn in whom the liver is insufficiently developed to be able to detoxify the bile pigment bilirubin. This situation is known as neonatal jaundice and can sometimes become a serious disease causing neurotoxic symptoms. Bilirubin is produced because of the degradation of haem:(protoporphyrin IX) iron(II) by haem oxygenase to give biliverdin which is reduced by biliverdin reductase to bilirubin. Tin-haem or dichloro(protoporphyrin IX)tin (IV) (structure **1**) is a potent inhibitor of haemoxidase.[156–170]

Hyperbilirubinaemia is also a symptom of other diseases such as congenital anaemias, thalassaemia and liver abnormalities. Tin-haem has been experimentally tested in animals[166] and humans[170–172] and has been found successful at suppressing the formation of the toxic metabolite bilirubin and in curing neonatal jaundice. In extensive toxicological studies in newborns (humans or animals) as well as in adults, tin-haem proved to be essentially innocuous. Pharmacological studies of this therapeutic agent are under development.



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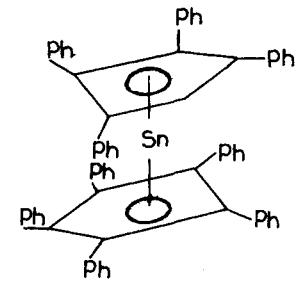

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4.2 Tin pharmaceuticals which are still being researched for possible use in humans

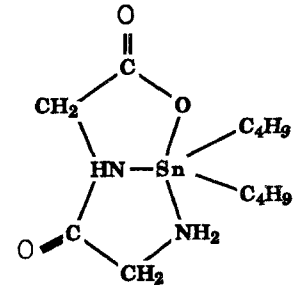
4.2.1 Cancer chemotherapy

Brown demonstrated in 1972 that the growths of malignant tumours in mice were appreciably retarded by feeding the animals with triphenyltin acetate.[173] The injection of this compound into the bloodstream had the same effect. Thereafter, several laboratories worldwide began investigations on antitumour activity of agents which were structurally analogous.

The first reported organotin compounds possessing some antitumour activity were organotin oxides (R_2SnO), diorganotin hydroxides ($R_2Sn(OH)X$], distannoxanes [$(XR_2Sn)_2O$] and di-(methylcarbonylmethoxides) [$R_2Sn(CH_2CO\text{-}Me)_2$], where R = alkyls, X = halogens.[174,175]

Another class of organotin compound which was extensively tested and which had a reproducible activity against P388 lymphatic leukaemia in mice had the general formula $R_2SnX_2L_2$ where L_2 is usually a bidentate ligand having oxygen and/or nitrogen donor atoms.[176–178] These compounds assume an octahedral structure (structure **2**).

The bidentate character of the L_2 compound ensures *cis* configuration for the two chlorine atoms. The highest activity is associated with these types of structure which are analogous to the *cis*-platinum antitumour drugs in which a



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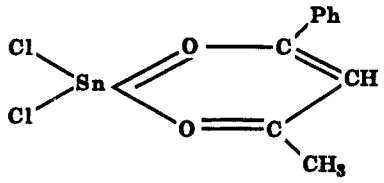

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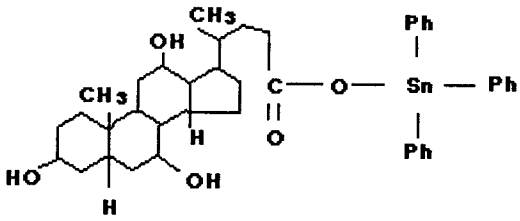

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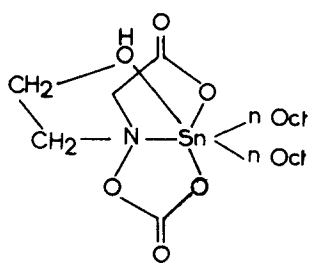
square planar microsymmetry around the platinum atom is connected with their antitumour activity. The existence of nitrogen and oxygen donor atoms as supporting ligands and *cis* leaving groups are necessary. It was also found in $R_2SnX_2L_2$ complexes that activity was associated with an average Sn–N bond length larger than 2.39 Å (0.239 nm). Inactive complexes have Sn–N distances lower than 2.39 Å. This finding suggested that active compounds have relatively weak Sn–N bonds and that possibly a predissociation mechanism is important for the antitumour activity.[179]

Analogous to some other metallocenes, decaphenyl stannocene $[\eta^5\text{-}(C_6H_6)_5C_5]_2Sn$ (structure 3) was found active against Ehrlich ascite tumours in mice, though the LD_{50} value for this compound is low.[180] This is one of the rather rare tin(II) anticancer compounds.



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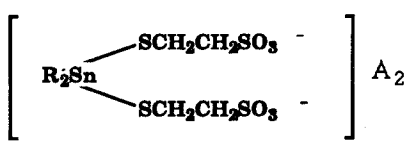

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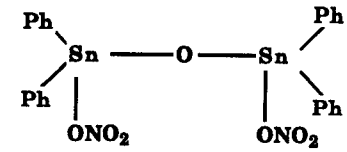

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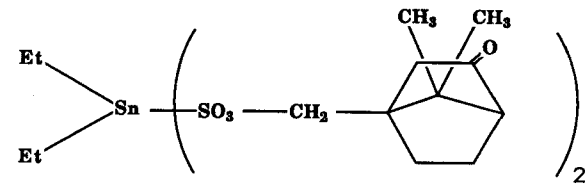

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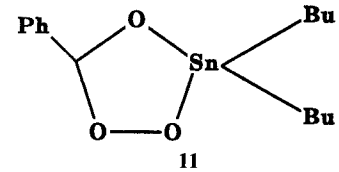

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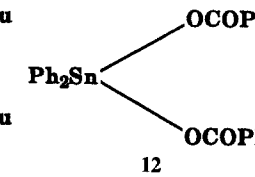

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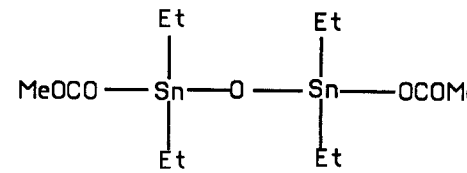

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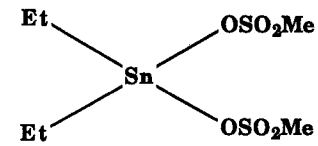

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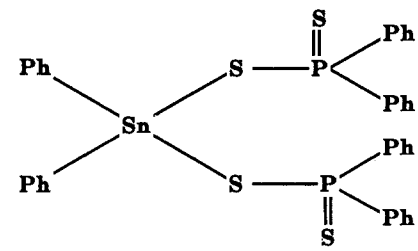

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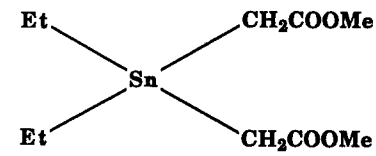

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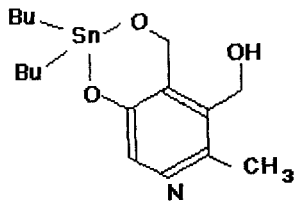

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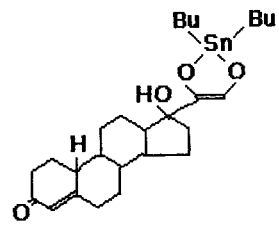

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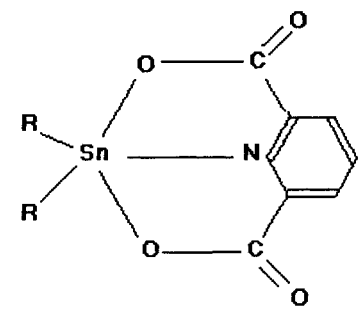
R = n-Bu, t-Bu, Ph



19

Complexes of tin(IV) with biologically important molecules were found to have positive activity *in vivo* against tumours. Adenine and glycylglycine[181,182] (structure **4**), a range of amino-acids, 2-mercaptoethanesulphate and purine-6-thiol[183] are all ligands forming such complexes.

Schiff base complexes of organotins are also active.[184] A successful agent against solid cancers such as the sarcoma 180 tumour in mice is dihalobis(benzoyl-acetonato)tin(IV)[185] (structure **5**).

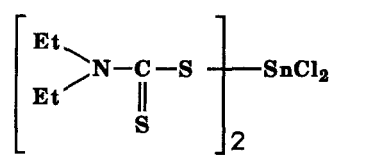
Some other compounds of general formulae $R_2SnX_2L_2$ have also been found to be active against tumour growth in mice,[186] with R = butyl and L_2 = phenanthroline, bipyridyl and histidine. Derivatives of steroids with organotins exhibit evidence of antitumour activity *in vivo* for mice, for example triphenyltin cholate screened against transplanted tumour fragments (mammary adenocarcinoma) in AK1 strain cancer-prone mice (structure **6**).[187,188] Diorganotin(IV) derivatives of iminodiacetic acid (structure **7**) are promising antitumour agents against P388 and L1210 leukaemias in mice.[189]

A major problem in the administration of active organotin compounds against malignant growth in test animals is the limited water solubility of some of the compounds. Some of the most soluble active organotin compounds have the general formula of structure **8**,[183] where $A = Na^+$ or $[C(NH_2)_3]^+$ and R = Me or Et. An active compound which is soluble is the dibutyltin-penicillamine complex $Bu_2Sn(pen)_2$.[183]

Several other compounds (structures **9–16**) have been tested by the USA National Cancer Institute and found to have over 50 % positive activity against malignant growth.[183]

There are many organotin compounds which are active against malignancy *in vitro*. A representative few are described. Gielen *et al.*[191] have prepared complexes of tin(IV) with pyridoxime (vitamin B_6) (structure **17**), with cortexolone (structure **18**), with erythromycin, and with 2,6-pyridine carboxylic acid (structure **19**).

These compounds were active *in vitro* against L1210 leukaemia (structure **17**), P388 leukaemia (structure **18**) and L1210 leukaemia, P388 leukaemia, and P815 leukaemias, B16 melanoma and Lewis lung carcinoma (structure **19**). Other antitumour organotin compounds of interest include the dichlorotin(IV) bis(diethyldithiocarbamates) (structure **20**), which were reported active against B16 melanoma and 3T3 fibroblast tumours *in vitro*.[192] Complexes of general formula $Sn(Rdtc)_2$, in which Rdtc are derivatives of carbodithioates, X = CH_2, O, S or NCH_3, (structure **21**) were also synthesized. These compounds display 50 % growth inhibition in relation to control values against KB cells *in vitro*.[193]



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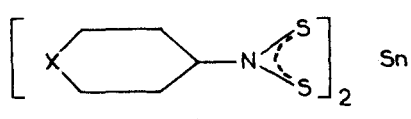


21

Tin(II) compounds, as well as mixed-valence tin(II)–tin(IV) compounds, have been found to be inactive against malignant cellular growth.[194]

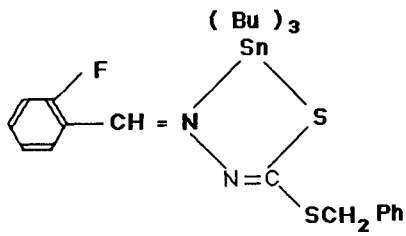
As previously noted, organotin(IV) compounds possess remarkable activity against a range of tumour types in mice. Although there is

Table 1 *Toxicity, lipophilicity and antitumour activity of R_2SnX_2 compounds*

	R_2SnCl_2		R_2SnX_2 or $R_2SnX_2L_2$[d]	R_3SnOH	
R	log *P*[a]	Cell viability, EC_{50}[b]	Antitumour activity, T/C (%)[c]	log *P*	Cell viability, EC_{50}
Methyl	−3.10	>120	120–135	−2.3	6
Ethyl	−1.40	>120	125–185	−1.8	2
n-Propyl	—	n.d.	120–160	—	—
n-Butyl	1.49	6–10	120–140	2.6	4
Phenyl	1.90	n.d.	120–182	2.65	4
n-Octyl	—	⩾100	—	—	—

[a] Logarithmic partition coefficient (n-octanol/water) used by Wong *et al.*[201] and Penninks *et al.*[195] showing hydrophilic (low-value) or lipophilic (high-value) properties.
[b] Effect of concentration in μM of xenobiotic agents which cause 50% cytotoxicity. In these experiments[199,200] rat thymocytes were used.
[c] T/C (%) is the median survival time of treated animals *versus* median survival time of control animals multiplied by 100, indicating anticancer activity; screening data for mice against P388 leukaemia.
[d] X = halogen, O, N, S; L_2 = bidentate ligand. Screening data for platinum carcinostats have T/C (%) values 300–400 against the same tumour type in mice.
— No data are reported.

no obvious correlation between structure and activity, almost all of the compounds reviewed possess the tetravalent tin moiety, R_2Sn^{2+}. There are some exceptions in that several active organotin compounds do not possess this moiety, e.g. structures **3**, **5**, **20** and **21** above, which are quite active and this is especially true for compound **3**. We can therefore conclude, in general, that the R_2Sn^{2+} moiety usually plays a significant role in the antitumour activity of the organotins, even though it is not always essential for anticarcinogenesis.



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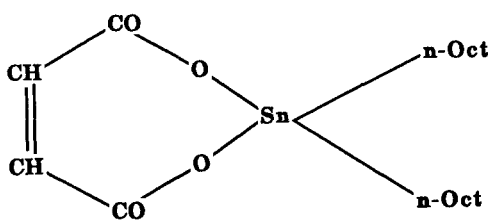

23

Among organotins, the dialkyl derivatives exhibit a greater antitumour activity than the corresponding mono-, tri- and tetra-alkyl derivatives.[195] The activity of the tri- or tetra-alkyl derivatives may be explained by their subsequent dealkylation *in vivo* which yields the corresponding active dialkyl derivatives. The half-life of this transformation for Bu_3SnF was found to be between 3.7 and 6.6 days.[196] If one ranks specific alkyl organotins in terms of the antitumour activity of the parent compounds, the diethyl and diphenyl derivatives have the highest activity *in vivo* provided that one takes no cognizance of their toxicities.[197] *In vitro* the relative activity of dialkyltins increases from dimethyls to dibutyls and then decreases to the higher dialkyls. The diphenyls have slightly lower activities than the diethyls. The toxicities of dialkyls parallel the same pattern.[195] Thus, a useful organotin antitumour agent ought to possess alkyls of low toxicity and of high activity. Such equilibria may be found among the butyls or phenyls and these alkyltins are the most popularly used in the synthesis of experimental antitumour tin drugs. There is a need to prepare more organotin antitumour agents containing the R_2Sn^{2+} moiety, cycloalkyl

radicals, or substituted aryl or other biologically active groups.[198]

The relative cytotoxicity of a range of xenobiotic agents may be measured from the extent of uptake of dyes through the xenobiotic damaged cell membranes in rat thymocyte cells. The data of Seinen *et al.*[199] and Vos *et al.*[200] has been reviewed by Penninks[195] for di- and tri-substituted organotin compounds. A definite correlation exists between cytotoxicity and lipophilicity,[78] where extremely hydrophilic or lipophilic agents are far less toxic, whereas the intermediate species display more toxicity. In Table 1 these findings are summarized for R_2SnX_2, $R_2SnX_2L_2$ and R_3SnCl compounds. Screening data for the first two types of compounds are also included.[197] The higher toxicity of analogues of R_3SnX compared with R_2SnX compounds is evident. The most lypophilic compound $(n\text{-}Oct)_2SnCl_2$ and the most hydrophilic compound (Me_2SnCl_2) are the least toxic to cells. The most active R_2SnX_2 or $R_2SnX_2L_2$ compounds against mice P388 leukaemia are those containing ethyl or phenyl radicals. The moderate toxicity of n-butyl organotins, correlated with an intermediate level antitumour activity, is also shown.

Accepting the hypothesis that R_2Sn^{2+} are the usual active species for the antitumour action of organotins, then a good antitumour agent should be easily dissociable following administration to the animals. This requires weak bonds which are readily hydrolysable between tin and the donor atom of the coordinated organic compound. Organic compounds coordinated to tin(IV) are therefore acting as R_2Sn^{2+} carriers to tumour cells. It might then be concluded, in conformance with Cardarelli's theory, that any exogenous tin is converted by the organism, in a mode which is reaction-rate-dependent, to the endogenous tin species that are anticarcinogenic. It is noteworthy that the kinetics of transfer and of the immediate action against the malignant cells could be limited by the speed of the biological process.

Another essential requirement for organotin antitumour activity is solubility. A successful drug ought to be soluble to facilitate administration either to the bloodstream or to the alimentary tract. The action of the R_2Sn^{2+} moiety against tumour cells has been thought to be analogous to that of the platinum (Pt^{2+}) carcinostats; this implies attack upon preferred loci of the DNA molecule forming intrastrand links[202] which modify or refold the DNA double helix.[131,203–205] The antitumour activity of organotins may also arise from changes in protein synthesis and in energy metabolism.[195]

These antitumour organotin agents, in spite of their widespread activity, have not yet been introduced for extensive clinical research or for tests involving humans. This is curious because the toxic effects usually associated with *cis*-platinum drugs in animals have not been observed to such an extent in the organotins. It is a well-known fact that the carcinostatic activities of the organotin compounds are lower than those for the *cis*-platinum range, but this is not regarded as a serious disadvantage in cancer chemotherapy.[206]

4.2.2 Tin compounds having a range of pharmacological applications

Before examining these compounds it is necessary to emphasize that their usage is not permitted for humans at present. All compounds examined are in the exploratory research stage. Of fundamental interest is the use of halo-organotins as anti-inflammatory agents against different types of oedemas in mice.[207,208] Compounds such as Bu_2SnCl_2 or Ph_3SnCl can inhibit oedemas as effectively as hydrocortisones.

Complexes of tin(II) with amodiaquine and primaquine (drugs derived from aminoquinolines) have schizonticidal activity and may have potential as antimalarials.[209] Organotin complexes with Schiff bases (structure **22**) have potential use as amoebicidal agents presenting activity on axenically grown *Entamoeba histolytica* and *tropozoites*.[210]

Some indole derivatives of 2-alkylindole, subsequent to complexation with organotins, have positive activity against *Bacillus subtilis*, *B. pumilus*, *Staphylococcus aureus* and *Micrococcus luteus*.[211] Organotin compounds have been tested against leishmaniasis[212] as well as against helminthes.[213] Dioctyltin maleate (structure **23**) has been tested against leishmaniasis in mice and dibutyltin dilaureate, distearate, dioleate, phenylethyl acetate and dipalmitate, act as antihelminthic agents in cats suffering from dipulidiosis (therapeutic dose of 300–400 mg kg^{-1}).

$SnCl_2$ or SnF_2 have been proposed for addition to bactericidal, fungicidal and viricidal preparations for veterinary use,[214] for antimicrobial use in humans,[215,216] in mixtures with benzophenanthridine alkaloid salts for the treatment of infection and diarrhoea, tooth diseases and possibly skin tumours and dermal fibrosarcomas, and for an antimicrobial role in cosmetics.[217,218] Vitamin supplements and diet

pills have been prepared containing phytosterol ethers and also fructose in which the carbon atom at C-6 has been substituted by Sn^{2+}.[219] the diet pills include antitrypsin. A very powerful agent for treating tapeworms, such as *Davainea proglottina*, in veterinary practice is Davainex 10, a tin derivative.[220]

It is possible to encounter many tin compounds in industry and agriculture as miticides, fungicides and molluscicides[221,222] without being aware of their pharmacological significance. For example, a comprehensive review of the industrial effects of organotin compounds, including many mentioned in this paper, has been published earlier.[97] A second review concerning the concentrations of tin in soil, plants, animals and man has just appeared.[101]

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